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HARMFULNESS OF HEADACHE MIXTURES.

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UNITED STATES DEPARTMENT OF AGRICULTURE,
BUREAU OF CHEMISTRY,
Washington, D. C., August 4, 1909.

SIR: Bulletin 126 of the Bureau of Chemistry reports the results of an investigation with regard to the harmful effects of acetanilid, antipyrin, and phenacetin. The data are there presented in detail and in a somewhat technical manner; hence it seems advisable, in view of the wide use of these agents in remedies sold without a physician's prescription, especially in headache mixtures, that the general public should be informed as to the nature of these drugs, their tendency to form habits, and their injurious effects, particularly their depressing action on the heart.

The beneficial effects of that provision of the food and drugs act which requires that the presence of certain powerful or dangerous ingredients of medicinal preparations shall be declared on the label are only fully obtained when the consumer is aware of the character of such ingredients and the ill effects which may be expected to follow their injudicious use. This brief résumé of the investigation is therefore presented in popular form as a matter of great importance to the general public, and its publication as a Farmers' Bulletin is recommended in order to insure the widest publicity.

Respectfully,

HON. JAMES WILSON,
Secretary of Agriculture.

H. W. WILEY,
Chief, Bureau of Chemistry.

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HARMFULNESS OF HEADACHE MIXTURES.

CHARACTER AND USE OF ACETANILID, ANTIPYRIN, AND PHENACETIN.

Acetanilid, antipyrin, and phenacetin are very commonly used in the preparation of mixtures intended for the relief of headache and other minor aches and pains. Thus there will often be seen upon the label of a headache powder, beneath the name of the preparation, a statement like the following: "Acetanilid, 240 grains per ounce." This means that each ounce of the preparation contains 240 grains of acetanilid, or, inasmuch as there are 480 grains in an ounce, that each powder is one-half acetanilid. Or the following may appear on the label: "Phenacetin, 120 grains per ounce," which means that each powder is one-fourth phenacetin. These drugs are white powders with comparatively little taste, and are often described together, as they are similar in many respects and have somewhat the same effects on the human body. They are known as coal-tar products for the reason that they are obtained indirectly from coal tar and possess the characteristics of the derivatives of that substance.

INTRODUCTION OF ACETANILID, ANTIPYRIN, AND PHENACETIN AS MEDICINES.

Acetanilid was introduced as a medicine in 1886. It had been known for many years before, but had possessed only a chemical and commercial interest. In the summer of 1886 a physician in one of the hospitals in Strassburg, Germany, noticed that the administration of acetanilid to a patient suffering from fever caused his temperature to fall. On giving the drug to other patients and finding that the fever was reduced in these cases also, he reported the results of his observations to other physicians, and this was the beginning of the use of acetanilid as a drug.

Antipyrin was introduced as a medicine in 1884. Its production was the result of chemical research, and for many years it was made according to a patented process.

The discovery of phenacetin in 1887 was also brought about by chemical investigation. It was the result of laboratory research, carried on with the object of discovering, if possible, some agent of the coal-tar class which would reduce fever, and, while possessing the desirable characteristics of acetanilid, be free from its undesirable effects. The object in view was only partially attained, however, for phenacetin possesses many of the harmful characteristics of acetanilid.

UNFAVORABLE SYMPTOMS PRODUCED.

The unfavorable symptoms produced by these drugs affect principally the heart and circulation and through them other parts of the body, and are generally observed as the result of their ill-advised use in the form of "patent" medicines for the relief of headache and other forms of pain. The symptom which occurs most frequently in poisoning by these drugs is blueness of the skin. If the dose taken has not been very large, the discoloration may be very slight and may affect only a small portion of the body. Thus in some persons who habitually use headache medicines containing these drugs, all that may be noted is an occasional blueness of the lips and mouth and possibly of the nails and finger tips. If, however, the doses are larger, or are taken more frequently, the blueness may affect the skin of the whole body. This peculiar effect was noticed by the physicians who first administered these remedies, when they were given in much larger doses than now, but little attention was paid to it, as it appeared to be a passing effect only. Since then, however, it has been learned that the bluing of the skin is not a harmless manifestation, but is due to destructive changes in the blood which are the direct result of the use of the drug, and that it is accompanied by impoverishment of the blood. Hence those who take these remedies habitually often suffer from "anemia," or thin blood, and the symptoms which usually accompany this condition—pallor, shortness of breath, palpitation of the heart, muscular weakness, disinclination to make any exertion, etc. The injudicious use of these remedies also has a harmful effect upon the heart, thus tending to exaggerate the symptoms above mentioned. In addition it may give rise to other ill effects which arise from weakness of the circulation.

OBJECTS FOR WHICH THESE DRUGS ARE USED.

As already stated, acetanilid, antipyrin, and phenacetin were at first used almost exclusively for the reduction of fever, but as time went on they were employed less and less for this purpose, because of their weakening effects, particularly upon the heart and circulation. They gradually came to be used more and more for the relief of pain, however, and to-day this constitutes their chief field of usefulness. During the time when they were used principally for reducing fever they were employed under the supervision of the physician and were administered with medical skill and judgment, but as their power to relieve pain has become better known they have been used more and more by the people generally, without medical supervision, for the relief of headache and other minor ills. At present they are extensively advertised and sold to be used in this way, largely in the form of so-called patent medicines. The injudicious use of these drugs has produced bad effects in many instances. Furthermore,

the number of reported cases of poisoning by at least one of them has increased notably during the last few years.

REASONS FOR THE INVESTIGATION.

Since the passage of the food and drugs act, June 30, 1906, the attention of the Department of Agriculture has been directed to this subject, particularly in connection with the proper labeling of drug products, and an attempt has been made to obtain full and reliable information with regard to the harmful effects of acetanilid, antipyrin, and phenacetin. While the majority of manufacturers have shown a disposition to comply with the law by naming upon the label the drugs enumerated in section 8 of the food and drugs act, and their derivatives and preparations, investigation shows that many medicines containing these or other dangerous agents bear statements which are not in harmony with the facts. The misrepresentation often takes the form of assertions to the effect that the remedy is harmless or that it contains no poisonous or harmful ingredients. Again, the public is given to understand in many cases that the medicine can be taken freely and safely until the desired effect is obtained. Some of the manufacturers of acetanilid preparations go even further and assert that the medicine, in addition to being an efficient remedy, acts as food or nourishment for the upbuilding of some particular part of the body; that it is, in short, a "nerve food" or a "brain food." Claims of this character are, however, without foundation, because so far as known there is no substance which acts as a food for one part of the body without acting as a food for the rest of the body as well. Moreover, as already stated, the frequently repeated or continued use of acetanilid tends to impair the nutrition of the body.

The purpose of this inquiry was not to depreciate in any way the value of these substances as medicines, but rather to furnish information to the public which would enable them to understand that, in the absence of reliable medical advice, these remedies should be employed with caution.

METHOD OF INVESTIGATION.

The investigation was conducted along two lines: (1) An inquiry was addressed to physicians in the United States with regard to their personal experience with these drugs in the practice of their profession. Nearly a thousand circular letters, each containing 18 questions, were sent out, and 400 replies were received. (2) A study was made of the cases of poisoning recorded in medical literature. Physicians often publish in medical periodicals descriptions of cases of poisoning observed by them in the course of practice, on account of the interest they possess for practitioners generally. Such cases are said to have been "reported" or "recorded."

SUMMARY OF RESULTS OF INVESTIGATION.

The results obtained in this investigation are summarized in the following table. Section A contains information with regard to a number of instances quoted in medical literature in which poisoning, death, or a drug habit has been known to result from the use of acetanilid, antipyrin, or phenacetin. The information set forth in Section B was furnished by the 400 physicians who replied to the circular letter issued by the Department. Nine hundred and twenty-five of these letters were sent out and, as already stated, 400 replies were received. Granting that the 525 physicians who did not reply had no cases to report, the question may profitably be asked, If 925 physicians have observed 814 cases of poisoning by these drugs, 29 deaths attributed to their use, and 136 instances of habitual use, how many such cases have in all probability been observed by the 125,000 physicians scattered throughout the United States? Section C gives the total of the cases recorded in medical literature added to those reported by the physicians.

Cases in which deleterious or fatal effects have been produced by acetanilid, antipyrin, and phenacetin.

A. CASES RECORDED IN MEDICAL LITERATURE, 1884-1907.

| Substance. | Poison- ing. | Deaths. | Habitual use. |
|-----------------|-----------------|---------|------------------|
| Acetanilid..... | 297 | 13 | 32 |
| Antipyrin..... | 488 | 10 | |
| Phenacetin..... | 70 | 3 | 1 |
| Total..... | 855 | 26 | 33 |

B. CASES REPORTED BY 400 PHYSICIANS, 1908.

| | | | |
|-----------------|-----|----|-----|
| Acetanilid..... | 614 | 17 | 112 |
| Antipyrin..... | 105 | 5 | 7 |
| Phenacetin..... | 95 | 7 | 17 |
| Total..... | 814 | 29 | 136 |

C. TOTAL OF COLLATED CASES (A AND B).

| | | | |
|--------------------|-------|----|-----|
| Acetanilid..... | 911 | 30 | 144 |
| Antipyrin..... | 593 | 15 | 7 |
| Phenacetin..... | 165 | 10 | 13 |
| General total..... | 1,669 | 55 | 166 |

INFORMATION FURNISHED BY PHYSICIANS.**CHANGE IN ATTITUDE OF PHYSICIANS.**

The replies to the circular letter indicate that while the use of these agents among the people generally has been increasing during recent years, their use by physicians has been decreasing. Sixty-six per cent of the physicians stated that they use acetanilid less frequently than formerly. Nearly 66 per cent made the same statement with

regard to antipyrin, and 51.2 per cent with regard to phenacetin. The reason given related in nearly every instance to the poisonous properties of these drugs, particularly their depressing effect upon the heart. The fact that they are poisons in the true sense of the word is generally recognized by physicians, but it is doubtful whether the people generally realize that they possess any harmful properties whatever. Certainly there is nothing to indicate an appreciation of this fact, if one can judge from the extent to which these drugs and the preparations containing them are used without the advice of a physician.

OPINIONS AND PRACTICE OF PHYSICIANS.

From the replies made to the more detailed questions sent to the physicians the following information was obtained:

Extent of use of these drugs (acetanilid, antipyrin, phenacetin) by physicians.—Thirty per cent of the physicians stated that they use acetanilid frequently or moderately, 28 per cent do not use it at all, and 25 per cent use it but rarely. Thirty-six per cent use phenacetin frequently or moderately, 23 per cent do not use it, and 21 per cent use it but rarely. Only 5 per cent use antipyrin frequently or moderately, 52 per cent do not use it, and 25 per cent use it but rarely.

Dose.—The replies to this question indicate that the doses prescribed to-day are much smaller than those formerly employed. The therapeutic committee of the British Medical Association made a report in 1894^a on this subject, and concluded that the ill effects which had been ascribed to these remedies were very largely the direct result of injudicious and excessive dosage. In harmony with this conclusion they suggested that these drugs should be used with greater caution in the future. Since that time the doses employed have been smaller than before, and it has been noted that coincidentally with this change the number of accidents resulting from taking these remedies has fallen off to a remarkable extent. A point of interest in connection with the subject of dosage and frequency of administration was brought out in a recent trial. The evidence showed that the directions for use accompanying many of these acetanilid preparations are not sufficiently definite to safeguard the patient against taking the medicine too frequently, and, in fact, that many of them advise a repetition of the dose until the desired result is obtained. An examination of a number of prescriptions for adults on file in various pharmacies in Washington, D. C., brought into court as evidence, supplied the following information on these points: (1) The average dose of acetanilid prescribed was 2.43 grains, and of phenacetin 1.92 grains; (2) the average interval between doses was 3.03 hours.

^a See British Medical Journal, 1894, vol. 1, page 85.

Relative harmfulness of these drugs.—Phenacetin was regarded as the least dangerous by 67 per cent of the physicians, acetanilid by 16 per cent, and antipyrin by 5 per cent. About 10 per cent considered one to be about as weakening to the system as the other.

Number of cases of poisoning by these drugs.—The number of cases of poisoning observed by the physicians who replied to this question was as follows: Acetanilid, 614 cases, 17 of which were fatal; antipyrin, 105 cases, 5 of which were fatal; and phenacetin, 95 cases, 7 of which were fatal.

Form in which drug was taken.—The replies showed that in 77, or 12 per cent, of the cases of poisoning, "patent" medicines containing acetanilid were taken and that in 44 per cent of the cases of habitual use of acetanilid, "patent" medicines containing this drug were employed.

Ailment for which medicine was taken.—In a large majority of cases (446 out of 720) the remedy was taken for headache. This was particularly true of acetanilid. This medicine was reported to have been taken for the relief of pain in 65 cases and for fever in 160.

It is not generally known that the application of acetanilid to the skin, either alone or in combination with some other powder like boric acid, may cause symptoms of poisoning. Nevertheless this is true. In 2.3 per cent of the cases of poisoning reported by physicians the ill effects followed the local use of this agent in the treatment of ulcers, burns, chafing, or some other form of skin trouble. A portion of the drug placed upon the diseased surface is absorbed through the skin and taken up in the body fluids and may produce unfavorable symptoms affecting the whole body. A number of cases of this kind have been recorded in medical journals, and brief abstracts of six of them may be found on pages 10 and 11.

Habitual use.—It has long been known that acetanilid, antipyrin, and phenacetin are habit-forming drugs, particularly acetanilid. The habit is usually acquired through the use of the remedy without the supervision of a physician for the relief of minor aches and pains, especially headache. Troubles of this kind are peculiarly likely to return again and again, and the remedy has but a temporary effect; hence the dose must be repeated, and in time the patient may become dependent upon the drug. Furthermore, the ache or pain for which the medicine was first taken is often worse than ever after the effects of the remedy have passed away, because of the weakened condition of the system which may result from the use of these agents, and hence there is additional call for the remedy. Thus a habit may be established—more drug, impaired bodily health, lessened resistance, more pain, more drug.

In reply to the inquiry by the Department, 112 instances of the acetanilid habit were reported, 7 of the antipyrin habit, and 17 of

the phenacetin habit. It should be remembered, however, that neither these cases nor those which are recorded in medical literature give an adequate indication of the extent to which these drugs are used habitually, inasmuch as only those cases have been reported in which the ill effects were so marked as to call for the services of a physician.

The principal symptoms which were reported by the physicians to have resulted from the habitual use of these agents were blueness of the skin, heart weakness, impoverishment of the blood, shortness of breath on exertion, nervous depression, sleeplessness, and loss of memory. In not a few cases the patients were reduced to a condition of invalidism.

Protracted ill effects.—Lasting ill effects were observed from the use of acetanilid in 38 cases, antipyrin in 2 cases, and phenacetin in 5 cases. The chronic symptoms most frequently noted were impoverishment of the blood, general weakness, nervousness, and weak and irregular heart action.

CASES OF POISONING RECORDED IN MEDICAL LITERATURE.

ACETANILID.

Number of cases recorded and their distribution.—From the time of the introduction of acetanilid as a medicine in 1886 until the end of the year 1907, about 300 cases of poisoning by this drug were recorded in medical publications. The exact number of cases could not be accurately determined because some of the physicians did not state definitely the exact number of cases they had seen. The cases were reported by 177 physicians, the number recorded for each year being as follows:

Cases of acetanilid poisoning recorded, 1886-1907.

| Year. | Number of cases. | Ratio to total cases in entire period. | Year. | Number of cases. | Ratio to total cases in entire period. |
|-----------|------------------|--|------------|------------------|--|
| | | <i>Per cent.</i> | | | <i>Per cent.</i> |
| 1886..... | 20 | 6.7 | 1898..... | 3 | 1.0 |
| 1887..... | 94 | 31.5 | 1899..... | 2 | .6 |
| 1888..... | 21 | 7.0 | 1900..... | 2 | .6 |
| 1889..... | 23 | 7.7 | 1901..... | 6 | 2.0 |
| 1890..... | 27 | 9.0 | 1902..... | 2 | .6 |
| 1891..... | 9 | 3.0 | 1903..... | 4 | 1.3 |
| 1892..... | 5 | 1.6 | 1904..... | 1 | .3 |
| 1893..... | 5 | 1.6 | 1905..... | 9 | 3.0 |
| 1894..... | 7 | 2.3 | 1906..... | 19 | 6.3 |
| 1895..... | 6 | 2.0 | 1907..... | 8 | 2.6 |
| 1896..... | 20 | 6.7 | | | |
| 1897..... | 4 | 1.3 | Total..... | 297 | |

Of the total number of cases recorded, 114, or more than one-third, were reported during the year and a half following the introduction of acetanilid as a medicine, and 185, or more than one-half, were reported during the first four and a half years of its history. The

occurrence of so many cases during this period was undoubtedly due in part to the fact that at this time the poisonous properties of acetanilid were not understood and its possibilities for harm were not known or appreciated. After the drug had been more thoroughly studied and its harmful effects in many cases had been brought to the attention of physicians, partly through personal experience and partly through reports published in the medical press, it was used with greater caution, especially when the patient showed signs of weakness. As a result the cases of poisoning decreased rapidly, and during the thirteen years following 1891 the number averaged less than 6 annually. Since the year 1904, however, there has been a notable increase in the number of cases reported, as well as in the number of deaths. This can be adequately explained only by the fact that during recent years the control of acetanilid as a medicine has rapidly passed from the hands of physicians to those of the people, owing largely to the extensive advertising of so-called patent medicines; and the increase in the number of cases reported and in the number of deaths is undoubtedly mainly due to the ill-advised use of remedies containing acetanilid by the general public for the relief of headache and other minor ills.

Fatalities.—Of the 297 cases of poisoning recorded, 13, or 4.4 per cent, terminated fatally. It is interesting to note that although 185, or 62.3 per cent, of all the cases that were recorded fell during the first four and one-half years of the history of acetanilid as a medicine, the number of deaths from acetanilid poisoning which occurred during this time was only 3, making the percentage of fatalities 1.6; whereas during the last three years, since the drug has been used more or less indiscriminately by the public, the percentage of fatalities recorded has been 16.6.

Discussion of symptoms and effects.—The fact that acetanilid when applied to the skin can give rise to symptoms of poisoning has already been mentioned. In 26, or 8.7 per cent, of the cases of poisoning by acetanilid recorded in medical literature the symptoms resulted from external application. These cases are of especial interest, as they afford a good illustration of the poisonous nature of the drug. In one of these cases the poisoning resulted fatally.^a The following abstract taken from a report by Gartman and Ball in 1897^b gives an illustration of the symptoms in this class of cases:

Child, 3½ years old. A scalded area of skin was dressed with 3 ounces of a 10 per cent ointment of acetanilid. Two days later 3 ounces were again applied, and the child began to turn blue. The color deepened until the skin and visible mucous membranes were of a blackish-blue color, and symptoms of collapse appeared. The ointment was discontinued and the symptoms gradually disappeared.

^a "Poisoning by acetanilid." Article by C. W. Rook in the *Journal of the American Medical Association*, 1896, vol. 26, p. 239.

^b "A case of acetanilid poisoning." Article in the *Philadelphia Polyclinic*, 1897, vol. 6, p. 381.

The symptom which appears most frequently in the recorded cases of poisoning by acetanilid is blueness of the skin, particularly of the finger tips, the nose and ears, and the lips and lining membrane of the mouth. Among the other symptoms observed are general weakness, dizziness, faintness, lividity of the face, a pinched and anxious expression, shortness of breath, great restlessness, sweating, coldness of the extremities, rapid and weak pulse, and, in severe cases, stupor and loss of consciousness. The habitual use of acetanilid is specifically mentioned in 32, or 10.8 per cent, of the recorded cases of poisoning.

The use of so-called patent medicines containing acetanilid is not mentioned in the reports of cases published during the eight years preceding the year 1905, but in the reports published during 1905 the use of these preparations is indicated in 55 per cent of the cases. In 1906 their use is indicated in 63.1 per cent of the recorded cases, and in 1907 in 87.5 per cent. Accompanying this rapid increase in the use of "patent" medicines containing acetanilid during recent years, which indicates a wider use of acetanilid by the general public, there has been an increase in the total number of cases of poisoning recorded, in the number of fatalities, and in the number of instances of habitual use.

Abstracts of acetanilid cases.—Following are brief abstracts of cases of poisoning by acetanilid taken from the reports published by physicians in medical periodicals. They illustrate the symptoms which are often observed in poisoning by this drug.

(1) Child, 6 weeks old: Frequent application of a powder consisting of equal parts of acetanilid and subgallate of bismuth to an inflamed area on the buttocks was followed by blueness of the skin of the entire body. (2) Boy, 2½ years: Similar powder dusted on a scalded surface caused blueness of lips, ears, and finger tips, extending to the entire skin, and symptoms of depression.—"Two cases of acetanilid poisoning in children from absorption from external wounds," by J. L. Manasses, in *International Medical Magazine*, New York, 1901, vol. 10, p. 278.

(1) A raw surface was copiously dusted with acetanilid. Next morning the patient was blue, collapsed, and unconscious. (2) Child, four months: Application of a powder consisting of one-half drachm of calomel and two drachms each of bismuth subgallate and acetanilid to the skin was followed by intense blueness of the skin.—"Toxic effects of acetanilid," by F. T. Stewart, in *Philadelphia Medical Journal*, 1901, vol. 8, p. 379.

Woman, 37: For eleven months she had dressed an ulcer of the leg with acetanilid, and during this time had run down in health and lost 70 pounds. Suffered from blueness of the skin, abdominal pain, general nervousness, shortness of breath, nausea and occasional vomiting, headache, and dizziness. Urine of a dark, amber tint. Examination showed impoverishment of the blood.—"A case of acetanilid poisoning from absorption," by R. M. Goepf, in *Journal of the American Medical Association*, Chicago, 1906, vol. 47, p. 359.

(1) Man, 38: Habitual use of acetanilid in the form of cephalgin for a year caused progressive loss of flesh and strength, somnolence, blueness of the skin, increasing weak-

ness, irritability of temper, and irregular heart action, the pulse becoming rapid on slight exertion. (2) Woman, 27: Habitual use of about 20 grains of acetanilid daily in the form of headache tablets caused progressive loss of health and strength, with blueness of the skin, shortness of breath, headache, palpitation of the heart, increasing rapidity of the pulse and respiration, especially on exertion, and deterioration in the quality of the blood.—“Chronic acetanilid poisoning; report of two additional cases,” by A. Stengel, in *Journal of the American Medical Association*, Chicago, 1905, vol. 45, p. 243.

A young woman, physically sound, had been taking orangeine powders for several weeks for sleeplessness. Her family noticed that her skin had a bluish tinge, and sent for a physician. He found the skin of face, lips, and extremities blue. She was also faint and chilly. Had taken 6 of the powders within eight hours. Her family promised that she should obtain no more, but three days afterwards she was found dead in bed in the morning. Coroner's verdict: “Death was from the effect of an overdose of orangeine powders administered by her own hand, whether accidentally or otherwise unknown to the jury.”—“Poisoning by orangeine,” by J. L. Miller, in *Journal of the American Medical Association*, Chicago, 1905, vol. 44, p. 1989.

(1) Man, 63: Chronic bronchitis and palpitation of the heart for two years. Pulse 160 and weak, becoming irregular upon exertion. Loss of appetite, constipation, blueness of the skin, varying in degree at different times. Had been addicted to the use of acetanilid for a year, taking 40 to 60 grains daily. Last two months he had been running down until he was confined to bed. Dose of acetanilid was reduced to 10 grains daily. He gradually improved and at end of a year was in fairly good health.

(2) Man, 32: Suffered from blueness of the skin, coldness of extremities, insomnia, impaired appetite, constipation, nervousness, and anemia. Urine, albuminous. Heart, rapid and feeble. Had been taking acetanilid for eight months, 12 to 40 grains daily, and his health had failed rapidly. The drug was entirely withdrawn and after a month he was in fairly good condition. After abstaining for eight months he again contracted the habit and his health again became impaired.—“A report of three cases of addiction to the coal-tar derivatives,” by J. S. Davis, in *American Medico-Surgical Bulletin*, 1894, vol. 7, p. 1490.

(1) Woman, 34: For six weeks she had suffered from dizziness, shortness of breath, loss of appetite, nausea, and severe headaches. Her physician found her unconscious, skin blue, and in profound collapse. Inquiry showed that she had been taking bromo-seltzer for two weeks in tablespoonful doses for pain. (2) Woman, 32: Use of headache wafers over a period of three weeks caused nausea and vertigo, attacks of fainting, blueness of the skin, loss of memory, and difficulty in concentrating the thoughts. Pulse, rapid, soft, and intermittent; urine scant. Convalescence lasted two months. (3) Woman, 39: Habitual use of headache powders containing 6 grains of acetanilid powder each, caused nausea, general nervousness and debility, blueness, and rapid intermittent pulse. (4) Woman, 69: Case similar to the preceding. (5) Woman, 36: Had been taking bromo-seltzer in tablespoonful doses for headache for two months. Collapsed in the street. Symptoms resembled those in preceding case.—“Acetanilid poisoning,” by E. L. Sutherland, in *Medical Sentinel*, Portland, Oreg., 1906, vol. 14, p. 466.

(1) Man, 40: Habitual use of acetanilid for two years caused gradual loss of health, blueness of the skin, general debility with loss of heart tone, and deterioration in the quality of the blood. (2) Man, 50: Habitual use of acetanilid for two years caused progressive loss of flesh and strength, the weight falling from 140 to 116, frequent vomiting, blueness of the skin, deterioration in the quality of the blood, mental dullness, and general debility amounting to invalidism.—“Chronic poisoning by acetanilid,” by D. D. Stewart, in *Journal of the American Medical Association*, Chicago, 1905, vol. 44, p. 1725.

Woman, 45: Habitual use of acetanilid in the form of Harper's brain food caused general malaise, drowsiness, fatigue on slight exertion, numbness of lower extremities, impaired locomotion, blueness of the skin, puffiness of the skin, tremor, and rapid pulse.—"Chronic acetanilid poisoning from Harper's 'brain food,'" by L. W. Glazebrook, in *Journal of the American Medical Association*, Chicago, 1907, vol. 49, p. 1673.

Man, 50: Habitual use of acetanilid, 30 to 40 grains daily, for six months caused a loss of 20 pounds in weight, blueness of face and mucous membranes, deterioration in the quality of the blood, and marked general weakness.—"Chronic cyanosis from acetanilid poisoning," by J. N. Hall and H. R. McGraw, in *Boston Medical and Surgical Journal*, 1903, vol. 149, p. 626.

ANTIPYRIN.

Number of cases recorded and their distribution.—The total number of cases of poisoning by antipyrin recorded in medical literature is approximately 488. They were reported by 299 physicians. Of the 488 cases, 10, or about 2 per cent, are reported to have resulted fatally. The distribution of the recorded cases by years from the time of the introduction of antipyrin as a medicinal agent, in 1884, to the end of the year 1907, is shown in the accompanying table.

Cases of antipyrin poisoning recorded annually.

| Year. | Number of cases recorded. | Number of observers. | Year. | Number of cases recorded. | Number of observers. | Year. | Number of cases recorded. | Number of observers. |
|-----------|---------------------------|----------------------|-----------|---------------------------|----------------------|-----------|---------------------------|----------------------|
| 1884..... | 33 | 19 | 1893..... | 13 | 10 | 1902..... | 4 | 4 |
| 1885..... | 68 | 28 | 1894..... | 16 | 16 | 1903..... | 8 | 8 |
| 1886..... | 48 | 18 | 1895..... | 28 | 17 | 1904..... | 7 | 6 |
| 1887..... | 37 | 27 | 1896..... | 13 | 13 | 1905..... | 3 | 3 |
| 1888..... | 55 | 41 | 1897..... | 31 | 20 | 1906..... | 5 | 5 |
| 1889..... | 24 | 18 | 1898..... | 22 | 11 | 1907..... | 2 | 2 |
| 1890..... | 22 | 8 | 1899..... | 2 | 2 | | | |
| 1891..... | 12 | 11 | 1900..... | 0 | 0 | Total.... | 488 | 299 |
| 1892..... | 34 | 11 | 1901..... | 1 | 1 | | | |

These figures indicate either that there has been a considerable falling off in the use of antipyrin during recent years, or that the drug has been employed with greater caution and discrimination, and undoubtedly both of these factors have played an important part in reducing the number of cases of poisoning.

Discussion of symptoms.—A review of the recorded cases of poisoning by antipyrin shows that in a number of instances a single dose of 5 grains or less has produced alarming symptoms in adults, while a dose of 10 or 15 grains has produced serious consequences. In many cases of harmful results the dose appears to have been neither unduly large nor long continued. From this it would appear that some persons are much more easily affected by antipyrin than others; in other words, the same dose may not affect one person unfavorably, but may produce serious symptoms of poisoning in another. This uncertainty of effect has undoubtedly been an important factor in bringing about a more cautious use of antipyrin by physicians. How much more cautiously should it be used, if at all by the people at large, without the supervision of a physician?

Abstracts of antipyrin cases.—The following abstracts of cases illustrate the symptoms which have been observed in cases of poisoning by antipyrin:

A dose of 10 grains of antipyrin in one case caused the appearance of an eruption resembling hives, and in another violent sneezing, swelling of the nose and throat, and shortness of breath.—“Peculiar susceptibility to the effects of antipyrin,” by E. Knight, in *British Medical Journal*, London, 1895, vol. 1, p. 1132.

The use of antipyrin was followed by the appearance of a bright red eruption over the body resembling that of scarlatina.—“Eruption from the use of antipyrin,” by Tisné, in *Journal de médecine de Paris*, 1888, vol. 15, p. 327.

(1) The taking of a teaspoonful of headache powder was followed by general itching, an eruption upon the skin, and marked depression. (2) A dose of 15 grains of antipyrin was followed by an eruption resembling that of measles, and great swelling of the face.—“Two cases of antipyrin rash,” by K. Löwy, in *Archiv für Dermatologie und Syphilis*, Vienna, 1904, vol. 68, p. 167.

(1) Boy, 9: The administration of 10 grains of antipyrin was followed by blueness of the skin and symptoms of collapse. (2) Symptoms of collapse followed the ingestion of two 10-grain doses of the drug. (3) Eruption resembling that of measles appeared after the use of antipyrin.—“Clinical value of antipyretics,” by L. J. Brooks, in *Medical Times*, Philadelphia, 1886–87, vol. 17, p. 794.

Paul Binet reported to the Medical Society of Geneva, September 5, 1888, a case in which a dose of 7.5 grains of antipyrin was followed by swelling of the eyelids, an itching eruption, nausea, dizziness, pain around the heart, and loss of consciousness.—Published in *Revue médicale de la Suisse romande*, Geneva, 1888, vol. 8, p. 635.

(1) Man, 32: Took 10 grains of antipyrin for headache. Within two minutes he was seized with alarming symptoms—a feeling of suffocation, swelling of the face so that the lids were closed, running of the eyes, and shortness of breath. The tongue was much swollen and the speech thick. There was no eruption. He was at work the next day with a slight swelling of the face. He had previously suffered from a similar attack, probably caused, as in this instance, by antipyrin. (2) Woman, 54: Ten grains of antipyrin caused temporary blindness, unconsciousness, convulsions, and symptoms of collapse.—“Notes on two cases of poisoning from antipyrin,” by D. G. Newton, in *Quarterly Medical Journal*, Sheffield, 1897–98, vol. 6, p. 133.

The ingestion of 5 grains of antipyrin by a young woman was followed by the appearance of an eruption resembling hives and disagreeable nervous symptoms, including excessive sneezing, shortness of breath, profuse sweating, coppery taste and smell, ringing in the ears, etc.—“Idiosyncrasy with regard to antipyrin: A warning,” by W. A. Sturge, in *British Medical Journal*, London, 1888, vol. 1, p. 243.

Woman, 53: A dose of 5 grains of antipyrin was followed by shortness of breath, an eruption resembling hives, swelling of the lips and tongue, unconsciousness, and symptoms of collapse. On the third day a white membrane formed upon the tongue, lips, and pharynx, and soon after 13 abscesses the size of a chestnut or smaller developed in the mouth. On two subsequent occasions the use of 5 grains of the drug was followed by similar symptoms.—“A case of antipyrin poisoning, with the formation of membranes in the mouth, and symptoms of *Laryngismus stridulus*,” by J. L. Salinger, in *American Journal of the Medical Sciences*, Philadelphia, 1890 (n. s.), vol. 99, p. 489.

PHENACETIN.

Number of cases and their distribution.—From the year 1887 to the close of 1907, 70 or more cases of poisoning by phenacetin were recorded in medical publications by 41 observers. Of the total

number of cases, 3, or 4.2 per cent, are reported to have terminated fatally. This number, 70, is notably less than the recorded number of cases of poisoning by either acetanilid or antipyrin, and this fact tends to substantiate the common belief that of the three drugs this is, under ordinary circumstances, the least likely to produce ill effects.

The number of cases of poisoning recorded in each year since the introduction of phenacetin as a medicine, together with the number of observers, is shown in the following table:

Cases of phenacetin poisoning recorded annually, 1887-1907.

[No cases recorded for years omitted.]

| Year. | Number of cases. | Number of observers. | Year. | Number of cases. | Number of observers. | Year. | Number of cases. | Number of observers. |
|-----------|------------------|----------------------|-----------|------------------|----------------------|-----------|------------------|----------------------|
| 1887..... | 1 | 1 | 1893..... | 2 | 1 | 1903..... | 1 | 1 |
| 1888..... | 23 | 10 | 1894..... | 3 | 3 | 1904..... | 2 | 2 |
| 1889..... | 11 | 6 | 1895..... | 6 | 4 | 1905..... | 2 | 2 |
| 1890..... | 6 | 3 | 1896..... | 1 | 1 | 1907..... | 1 | 1 |
| 1891..... | 5 | 2 | 1899..... | 1 | 1 | | | |
| 1892..... | 4 | 2 | 1901..... | 1 | 1 | Total . | 70 | 41 |

It will be seen that 23, or 32.8 per cent, of all the cases were recorded during the year following the introduction of phenacetin as a medicine in 1887, and that 40, or 57.1 per cent, were recorded during the years 1888, 1889, and 1890. The large proportion of cases recorded during this period was undoubtedly due in part, as in case of acetanilid and antipyrin, to the fact that at this time the depressing effect of phenacetin was not fully appreciated. After the year 1890 the number of cases of poisoning recorded annually was, on the average, only two or three cases, and the number appears to have decreased rather than increased as the years passed.

Discussion of symptoms.—The ill effect which appears to occupy the place of greatest importance in the recorded cases of poisoning by phenacetin is general weakness. Other symptoms noted were vomiting, blueness of the skin, rapid and weak pulse, shortness of breath, cold perspiration, great restlessness, an eruption on the skin, and disturbance of the action of the kidneys.

Abstracts of phenacetin cases.—The following abstracts illustrate the symptoms in cases of poisoning by phenacetin:

Woman: Had been addicted to the phenacetin habit for about seven months, daily quantity being between 15 and 20 grains. Addiction was discovered by her husband when her supply of the drug gave out and the local pharmacist also ran out of a supply temporarily. Violent convulsive and hysterical seizures followed and continued until phenacetin was secured for her. Pulse, 170, and very weak. Respiration rapid and spasmodic. Pupils widely dilated; pallor, cold perspiration. She had more than a dozen convulsions and vomited freely. Before beginning the habit she was "a healthy, buxom country girl." Examination made after the attack above described showed some anemia, complexion bad, circulation weak, pulse 124, sleep restless and troubled,

digestion impaired, occasional vertigo.—“A report of three cases of addiction to coal-tar derivatives,” by J. S. Davis, in *American Medical and Surgical Bulletin*, 1894, vol. 7, p. 1490.

Boy, 17: After taking 15-grain doses of phenacetin for headache for three weeks, a dose caused vomiting, followed on the next day by great weakness, blueness of the face, weak pulse, and diarrhea. Jaundice followed, and the blueness spread to the extremities. The urine consisted of almost pure blood. Death occurred after two days.—“Phenacetin poisoning with fatal result,” by G. Krönig, in *Berliner klinische Wochenschrift*, 1895, vol. 32, p. 998.

Woman, 34: Soon after taking 15 grains of phenacetin she felt dizzy, cold, and nauseated. Her headache became worse, and after three hours she took another phenacetin powder. This was followed by an aggravation of the symptoms; the nausea and sensation of chilliness increased, the hands, lips, and cheeks were deep blue, and there was cold perspiration and shortness of breath.—“Distressing poisonous side-effects of phenacetin,” by Lindmann, in *Therapeutische Monatshefte*, Berlin, 1888, vol. 2, p. 307.

On Friday, December 13, 1907, at 9.20 p. m., a girl of 16.5 years, in good general health, but having a headache and feeling that she had taken cold, took 2 headache tablets and went to bed. Later, her mother heard her coughing and went to her. There was nothing at this time to cause alarm, but a little before 11 o'clock the girl's lips and face began to become blue, and in consequence a physician was sent for. He responded at once, and found the girl with great weakness of the heart. Before he could administer any remedy she was dead.

The box with the remaining tablets was sent to the office of the state board of health for examination. The tablets were found to contain phenacetin.—“Fatal poisoning by phenacetin in headache tablets,” by George L. Tobey, in *Monthly Bulletin of the State Board of Health of Massachusetts*, January, 1908.

The taking of 15 grains of phenacetin every two hours for twenty-four hours was followed by extreme weakness and then by symptoms of collapse, with tendency to fainting, dizziness, shortness of breath, blueness of the hands and feet, pain around the heart, nausea, and a rapid and feeble pulse. The skin was of a yellowish gray color and the next day an eruption appeared. Recovery after five days.—“Contribution to the study of the poisonous nature of phenacetin,” by J. Meurice, in *Annales de la société de médecine de Gand*, 1905, vol. 85, p. 199.

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